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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,959	12/15/2003	Karin Drechsel	1/1156-1-C1	3400

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,959	DRECHSEL ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 38-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31, 38-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Amendments and Remarks filed on 11/07/05. No claims have been cancelled and no new claims have been added. Accordingly claims 1-31 and 38-95 remain pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 and 38-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While specification discloses broad pH range of "between 2.0 and 4.5" and an upper limit of 3.1, there is no disclosure of the specific ranges of "between 2.0 and 3.1", "between 2.5 and 3.1", "between 2.7 and 3.1" and "between 2.7 and 3.0" as recited in the amended claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-31, 50, 53-80 and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Freund et al (DE 19653969)(US 2001/0008632 is being used as the translation for the German document).

Freund teach pharmaceutical preparations in the form of aqueous solutions for the production of propellant-free aerosols for inhalation for the therapy of obstructive lung diseases. Pharmaceuticals intended for inhalation are dissolved in an aqueous or ethanolic solution or a solvent mixture of ethanol and water. The amount of dissolved pharmaceutical in the preparation is between 0.001 and 30%, and preferably between 0.05 and 3%. All substances which are suitable for application by inhalation and which are soluble in the specified solvent can be used as pharmaceuticals in the new preparation. Of especial interest are betamimetics, anticholinergics, antiallergic, antihistamines and steroids, as well as combinations of these active ingredients (sections [0001] to [0007]).

Freund teaches that addition of an effective amount of a complexing agent, such as, EDTA, citric acid, ascorbic acid and their salts, and more especially disodium salt of ethylenediaminetetraacetic acid, eradicates the problem of spray anomalies. The effective quantity of complexing agent Na-EDTA is between 10 and 100 mg/100 ml. Also if necessary, ethanol can be added to increase solubility up to 70% by volume. Other adjuvants such as preservatives, especially benzalkonium chloride can be added in amounts of between 8 and 12 mg/100 ml (sections [0009] to [0013]).

Freund discloses a list of compounds which can be used as active ingredients, singly or in combination, in the aqueous pharmaceutical preparation. In individual cases, it may be required to add a higher quantity of ethanol or a solution mediator to improve solubility. The list includes; tiotropium bromide, budesonide, beclomethasone, disodium cromoglycate, etc. The solutions are set to a pH of 3.2 to 3.4 with 0.1 or 1 N HCL in 100 ml of finished preparation (see sections [0014] to [0046] and [0055]).

Claims 1-19, 23-30, 50, 53-70, 73-80 and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Bozung et al (DE 19921693)(the US patent 6,433,027 is being used as the translation for the German document).

Bozung et al teach medicament compositions based on anticholinergic compounds which have a long-lasting effect and betamimetics, which have a long-lasting effect, processes for their production and their use in the therapy of respiratory ailments, especially COPD (col. 1, lines 11-16). Tiotropium bromide monohydrate is the preferred anticholinergic (col. 5, lines 51-55). The medicaments for inhalation are dissolved in an aqueous or ethanolic solution, wherein solvent mixtures of ethanol and water are also suitable. Other adjuvants, such as preservatives, e.g. benzalkonium chloride in concentration range of 8 to 12 mg/100 ml are added. Complex formers like EDTA, citric acid, ascorbic acid can be added. The formulations have a pH of 3.4 and the medicament is present in an amount of 0.001 to 5% (see col. 6, line 39 to col. 7, lines 17-40).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38-49, 51, 52, 81-92, 94 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al as applied to claims 1-31, 50, 53-80 and 93 above, and further in view of Weston et al (WO 9114468).

Freund et al, discussed above, lacks specific teachings on the inhalation device.

Weston et al discloses a metered dose inhaler which incorporates metering means for metering a quantity of fluid, and the atomizing means is provided by a mechanical break up device through which the metered quantity of fluid is passed to atomise it when it is subject to said increase in pressure (page 7, lines 5-9). For dispensing a spray of an aqueous solution of a medicament for inhalation into lungs, the droplet size is desirably less than 10 micrometers, typically 2 to 6 micrometers.

Weston also discloses that very high pressures can be generated in the pump cylinder or pressure and nozzle orifice diameters can be used, for example up to 100 micrometers, typically greater than 30 to 50 micrometers. The preferred pressures are from 50 to 400 bar, and more preferably from 100 to 350 bar with nozzle orifice of from 1 to 12 micrometers (page 12, lines 1-32).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have utilized the preparation of Freund et al by incorporating it in a device suitable for such preparations and because it is made simpler in design and cheaper to produce and suited to its function, as taught by Weston et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-31 and 38-95 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-81of U.S. Patent No. 6,890,517 B2. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the examined claims are anticipated by the reference claims. Claims 1-31 and 38-95 are generic to all that is recited in claims 1-81 of U.S. Patent No. 6,890,517 B2. That is, claims 1-81of U.S. Patent No. 6,890,517 B2 fall entirely within the scope of claims 1-31 and 38-95. Specifically, the pharmaceutical preparation comprising tiotropium or a salt thereof, a solvent, a preservative and an acid to achieve or maintain a pH of between 2.0 and 4.5, recited in claim 1 of instant Application is substantially the same as the formulation stated in claim 1 of the U.S. Patent No. 6,890,517 B2. The difference is that claim 1 of U.S. Patent No. 6,890,517 B2 additionally recites a second active agent. The open language of "comprising" used in the instant claim 1 allows for other agents being added to this formulation, thus it is considered that the scope of both claims are the same. The depending claims of both the Application and the U.S. Patent appear to be substantially the same.

Claims 1-31, 50, 53-80 and 93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,908,928 B2 in view of Freund et al (US 20010008632). Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims would have been obvious over the reference claims. Here, claim 1 recites a pharmaceutical preparation comprising tiotropium or a salt thereof, a solvent, a preservative and an acid to achieve or maintain a pH of between 2.0 and 4.5. Claims of U.S. Patent No. 6, 908,928 B2 recite a pharmaceutical composition comprising an effective amount of tiotropium bromide monohydrate, and a method of treating a

disorder by administering the said formulation. Freund et al teaches formulations comprising active agents such as tiotropium, a solvent, Ph adjuster and a preservative. It would have been obvious to one of ordinary skill in the art to have modified the formulations of Us Patent No. 6,908,928 B2 by employing the specifics of pharmaceutical formulations as taught by Freund et al with reasonable expectations of successfully preparing an effective formulation for inhalation.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure, Jaeger et al (5,964,416).

Jaeger et al teaches a device adapted for use in an atomizer to produce an inhalable aerosol of a liquid medicament without the use of propellant gas. The atomizer is preferably a metered dose inhaler the hollow piston with valve member exerts a pressure of about 50 to 600 bar on the fluid at its high pressure end at the moment of release of the spring. The nozzle is microstructured and consists of two plates of glass and/or silicone firmly joined together, of which at least one plate has one or more microstructured channels which connect the nozzle inlet end to the nozzle outlet. At the nozzle outlet end is at least one circular or non-circular opening less than or equal to 10 micron in size. In a nozzle member having at least two nozzle openings at the outlet end, the directions of spray may be inclined relative to one another at an angle from 20 to 160 degrees (col. 5, lines 25-53).

Response to Arguments

Applicant's arguments filed 11/07/05 have been fully considered but they are not persuasive.

Applicant argues that Freund and Bozung do not teach "each and every element as set forth in the claims". Applicant, however does not identify or refer to any specific elements missing in the two cited references. Freund teaches formulations comprising: 1- an active agent, tiotropium bromide in an amount of from 0.001 to 30% ; 2- an ethanolic/aqueous solvents; 3-an acid to adjust the pH and 4- a preservative, specifically benzalkonium chloride. Freund also teaches that such formulations can be used to treat COPD.

Bozung teaches formulations comprising tiotropium bromide for treating respiratory ailments such as COPD. The formulations may comprise benzalkonium chloride, HCL (1N), EDTA and a solvent including water or a mixture of water and ethanol.

Thus as shown each and every element of the instant claims are taught by the references cited.

Applicant argues that neither Freund nor Watson "suggest or even hint to one of ordinary skill in the art, much less with the required reasonable expectation of success, of the claimed composition of applicant's invention". This argument is not persuasive. As shown above, Freund clearly teaches the formulations and their use in treating COPD and other respiratory ailments. It is clear to one of ordinary skill in the art that

administration of aerosol formulations require a device. Watson teaches the suitable device.

Applicant argues, by showing in a Diagram of "Decomposition of tiotropium bromide at different pH values", that the formulations are more stable at pH values of 3.0. The diagram shows that there is a relationship between pH levels and the decomposition levels of the tiotropium bromide. Specifically, it shows that the lower the pH levels, the less decomposition. Instant claims require a pH value of 3.1 and the prior art teaches a pH value of 3.2. The two pH values are close enough for one of ordinary skill in the art to make and use the formulations as taught or claimed. Furthermore the criticality of any specific pH value is not shown here.

Applicant, with regard to the Double Patenting rejections, states that "in view of the arguments outlined in the paragraph above with reference to the unexpected activity of the preparation at the pH levels claimed, Applicants believe that the rejection is rendered moot". This is not persuasive because as shown above Freund and Drechsel et al do teach the required elements of the instant claims and the Double Patenting rejections are proper and thus maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary L. Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mina Haghighatian
February 13, 2006

STEENBAKAMADHAN
SUPERVISORY PATENT EXAMINER